# SURVIVAL AND PROGNOSTIC FACTORS AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA IN HOSPITAL PAKAR UNIVERSITI SAINS MALAYSIA

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# SURVIVAL AND PROGNOSTIC FACTORS AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA IN HOSPITAL PAKAR UNIVERSITI SAINS MALAYSIA

**by**

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## LIST OF SYMBOLS

| | |
|---|---|
| < | Less than |
| > | More than |
| ≤ | Less than or equal to |
| ≥ | More than or equal to |
| α | Alpha / level of significance |
| b | Regression coefficient |
| = | Equal |
| n | Number of samples |
| & | Percentage |
| A | Accrual time during which patients were recruited |
| df | Degree of freedom |
| F | Additional follow up time after end of recruitment |
| 1-β | Power |
| m | Ratio of control to experimental patients |
| m1 | Median survival time on control treatment |
| *p* | probability |

## LIST OF ABBREVIATIONS

| | |
|---|---|
| BCLC | Barcelona Clinic Liver Cancer |
| CI | Confident interval |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis V virus |
| HR | Hazard ratio |
| INR | International Normalized Ratio |
| LML | Log minus log |
| LR | Likehood ratio |
| OR | Odds ratio |
| OS | Overall survival |
| PH | Proportional Hazard |
| PS | Power and sample calculation |
| PVT | Portal vein thrombosis |
| R | Detectable hazard ratio |
| RFA | Radiofrequency ablation |
| SD | Standard deviation |
| SE | Standard error |
| SPSS | Statistical package for Sosial Sciences |
| STATA | Statistics/ data analysis |
| t | time |
| TACE | Transarterial chemoembolization |
| TNM | Tumor-node-metastasis |
| WHO | World Health Organization |
| USM | Universiti Sains Malaysia |

## LIST OF APPENDICES

**KELANGSUNGAN HIDUP DAN FAKTOR PROGNOSTIK DALAM KALANGAN PESAKIT KARSINOMA HEPATOSELULAR DI HOSPITAL PAKAR USM**

## ABSTRAK

**Pengenalan**: Karsinoma hepatoselular (HCC) adalah kanser keenam paling kerap di dunia, dengan lebih daripada 800,000 kes baharu didiagnosis setiap tahun. Kajian mengenai kadar kelangsungan hidup dan prognostik adalah penting untuk meningkatkan keberhasilan rawatan pesakit, memandangkan pengesanan awal dan strategi rawatan yang berkesan masih terhad, yang memberi kesan kepada beban global penyakit ini. **Objektif**: Objektif kajian ini adalah untuk menentukan masa kelangsungan hidup median bagi pesakit HCC, membandingkan masa kelangsungan hidup median antara kumpulan berdasarkan faktor sosio-demografi, ciri klinikal, penemuan makmal, dan modaliti rawatan, serta mengenal pasti faktor prognostik yang dikaitkan dengan kelangsungan hidup dalam kalangan pesakit HCC di HPUSM. **Metodologi**: Kajian tinjauan rekod retrospektif telah dijalankan melibatkan 240 pesakit yang didiagnosis dengan HCC di HPUSM, Kelantan. Fasa pengambilan data adalah dari 1 Januari 2012 hingga 31 Disember 2021 berdasarkan kriteria inklusi dan eksklusi. Tempoh susulan tambahan adalah dari 1 Januari 2022 hingga 31 Disember 2023 (24 bulan). Rekod perubatan terperinci dikaji oleh seorang penyelidik dan semua maklumat penting berkaitan pemboleh ubah yang dikaji serta status kelangsungan hidup pesakit sehingga 31 Disember 2023 telah dikumpul dan direkodkan ke dalam borang pengumpulan data. Analisis data dilakukan menggunakan regresi bahaya berkadar Cox dan anggaran Kaplan-Meier. **Keputusan**: Penemuan kajian ini menunjukkan bahawa sejumlah 199 (92.1%) pesakit meninggal dunia akibat HCC dan

komplikasinya. Masa kelangsungan hidup median keseluruhan bagi pesakit HCC dalam kajian ini adalah 9 bulan (95% selang keyakinan (SK): 7.0, 13.0) manakala kadar kelangsungan hidup satu tahun keseluruhan adalah 44.1% (95% SK: 37.0, 52.0). Tiada perbezaan yang signifikan dalam kelangsungan hidup median berdasarkan faktor sosio-demografi. Walau bagaimanapun, ciri klinikal seperti dislipidemia ($p=0.027$), hepatitis virus ($p=0.036$), sirosis hati ($p=0.008$), kesakitan abdomen, distensi abdomen, hilang selera makan, penurunan berat badan, hepatomegali, kelas Child-Pugh, saiz tumor, dan trombosis vena portal (semua $p<0.001$), serta jaundis ($p=0.002$), menunjukkan hubungan yang signifikan dengan kelangsungan hidup. Penanda makmal termasuk Alfa-fetoprotein, Aspartat transferase, Alkalin fosfatas, bilirubin, dan Nisbah Normalisasi Antarabangsa (semua $p<0.001$) juga mempunyai nilai prognostik yang ketara. Selain itu, kaedah rawatan juga memberi kesan signifikan terhadap kelangsungan hidup ($p<0.001$). Setelah disesuaikan untuk pemboleh ubah lain, faktor prognostik signifikan yang mempengaruhi kelangsungan hidup dalam HCC adalah jantina (Nisbah bahaya terselaras (NBT): 0.64; 95% SK: 0.44, 0.95), viral hepatitis virus HCV (NBT: 0.60; 95% SK: 0.39, 0.90), kesakitan abdomen (NBT: 1.53; 95% SK: 1.12, 2.10), hilang selera makan (NBT: 1.49; 95% SK: 1.03, 2.16), splenomegali (NBT: 1.69; 95% SK: 1.11, 2.55), Child Pugh kelas B (NBT: 1.80; 95% SK: 1.28, 2.52), dan Child Pugh kelas C (NBT: 2.74; 95% SK: 1.78, 4.21), Alfa-fetoprotein (NBT: 1.62; 95% SK: 1.13, 2.31), Aspartat transferas (NBT: 1.55; 95% SK: 1.12, 2.14), Alkalin fosfatas (NBT: 1.56; 95% SK: 1.14, 2.13), rawatan tunggal (NBT: 0.24; 95% SK: 0.10, 0.56) dan rawatan pelbagai (NBT: 0.16; 95% SK: 0.07, 0.38). **Kesimpulan:** Masa kelangsungan hidup median dan kadar kelangsungan hidup satu tahun bagi HCC berada dalam julat yang dilaporkan di negara-negara Asia yang lain. Walaupun faktor sosio-demografi tidak menunjukkan kesan yang signifikan, ciri

klinikal, peningkatan biomarker, dan modaliti rawatan merupakan faktor prognostik utama. Faktor prognostik signifikan yang dikenalpasti dalam kajian ini secara amnya serupa dengan kajian lain.

**Kata kunci:** Karsinoma hepatoselular, masa kelangsungan hidup median, kadar kelangsungan hidup 1-tahun, faktor prognostik

**SURVIVAL AND PROGNOSTICS FACTORS AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA IN HOSPITAL PAKAR UNIVERSITI SAINS MALAYSIA**

## ABSTRACT

**Introduction**: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with over 800,000 new cases diagnosed annually. Studying survival and prognostic rates is crucial to improving patient outcomes, as early detection and effective treatment strategies remain limited, impacting the global burden of this disease. **Objectives**: The objectives of this study were to determine the median survival time of patients with HCC, compare median survival times across groups based on sociodemographic factors, clinical characteristics, laboratory findings, and treatment modalities, and identify prognostic factors associated with survival among HCC patients in HPUSM. **Methodology**: A retrospective record review study was conducted involving of 240 patients diagnosed with HCC in HPUSM, Kelantan. Recruitment phase was from 1st January 2012 to 31st December 2021 based on inclusion and exclusion criteria. An additional follow up period was from 1st January 2022 until 31st December 2023 (24 months). Detailed medical records were reviewed by a researcher and all the important information on the variable of interest and patients' survival status until 31st December 2023 were collected and recorded into a data collection form. Cox proportional hazard regression and Kaplan Meier estimator were used for the data analysis. **Results**: The finding of this study showed that a total of 199 (92.1 %) patients died due to HCC and its compilation. The overall median survival time for patients with HCC in this study was 9 months (95% CI: 7.0 – 13.0) and the overall one-year survival rate for patients with HCC was 44.1 % (95% CI:

37.0, 52.0). No significant differences were observed in median survival based on sociodemographic factors. However, clinical characteristics such as dyslipidemia (p=0.027), viral hepatitis (p=0.036), liver cirrhosis (p=0.008), abdominal pain, abdominal distension, loss of appetite, weight loss, hepatomegaly, Child-Pugh class, tumor size, and portal vein thrombosis (all p<0.001), as well as jaundice (p=0.002), were significantly associated with survival. Laboratory markers, including Alpha-fetoprotein, Aspartate transferase, Alkaline phosphatase, bilirubin, and International Normalized ratio (all p<0.001), also showed significant prognostic value. Additionally, treatment modalities significantly influenced survival (p<0.001). After adjusting for other variables, the significant prognostic factors that influenced survival in HCC were gender (Adjusted hazard ratio (AHR): 0.64; 95% CI: 0.44, 0.95), viral hepatitis HCV (AHR: 0.60; 95% CI: 0.39, 0.90), abdominal pain (AHR: 1.53; 95% CI: 1.12, 2.10), loss of appetite (AHR: 1.49; 95% CI: 1.03, 2.16), splenomegaly (AHR: 1.69; 95% CI: 1.11, 2.55), Child Pugh class B (AHR: 1.80; 95% CI: 1.28, 2.52), and Child Pugh class C (AHR: 2.74; 95% CI: 1.78, 4.21), Alpha-fetoprotein (AHR: 1.62; 95% CI: 1.13, 2.31), Aspartate transferase (AHR: 1.55; 95% CI: 1.12, 2.14), Alkaline phosphatase (AHR: 1.56; 95% CI: 1.14, 2.13), single treatment (AHR: 0.24; 95% CI: 0.10, 0.56) dan multiple treatment (AHR: 0.16; 95% CI: 0.07, 0.38). **Conclusion**: The median survival time and one-year survival rate for HCC falls within the range reported in other Asian countries. While sociodemographic factors had no significant impact, clinical characteristics, elevated biomarkers, and treatment modalities were key prognostic factors. The significant prognostic factors that identified in this study were considerably similar with other studies.

**Keywords:** Hepatocellular carcinoma, median survival, one-year survival rate, prognostic factors

# CHAPTER 1

# INTRODUCTION

## 1.1 Incidence of cancer

The incidence of cancer has been increasing over the years, and efforts to reduce its burden have been ongoing for decades (Teh & Woon, 2021). The rising number of cancer cases poses a significant health challenge, placing substantial physical, emotional, and financial strain on patients, communities, and the healthcare system (Cancer.net, 2022). According to the World Health Organization (2021), Malaysia recorded 48,639 new cancer cases in 2020, which increased to 51,650 cases in 2022. In the same year, the total number of cancer-related deaths in Malaysia was 31,633 cases (Globocan, 2022). Furthermore, the incidence of cancer in Malaysia is projected to double by 2040 (WHO, 2021).

Liver cancer significantly contributes to the global cancer burden, with rising incidence rates observed in numerous countries in recent decades (McGlynn K.A., Petrick J.L., *et al.*, 2020). Emerging as a substantial global health challenge, it is anticipated to surpass 1 million cases by 2025. In Malaysia, it ranks as the sixth most common cancer, with 2,149 new cases reported in 2020. Older persons are at higher risk and there is male predominance observed. The age-standardized incidence rate (World) is 9.3 per 100,000 for males and 3.6 per 100,000 for females. Liver cancer is also the third leading cause of cancer-related deaths in Malaysia, with 2,050 deaths in 2020. It has a high mortality rate, with an age-standardized mortality rate (World) of 6.4 per 100,000 for male and 6.1 per 100,000 for female. It has a low 5-year prevalence, with only 2,267 cases in 2020. This indicates that most patients do not survive long after diagnosis (Globocan, 2021). Most liver cancers are hepatocellular

carcinoma (HCC), which arising from malignant hepatocytes and accounts for about 90% of all cases (Llovet J.M., *et al.*, 2021).

Survival rates in HCC exhibit variability based on the causative risk factors (Calderon-Martinez E., and Landazuri-Navas S., *et al.*, 2023). Globally, numerous studies have sought to identify predictive factors for HCC survival outcomes. Investigations into HCC survival in Asian countries have yielded diverse results (Hassanipour S., and Vali M., *et al.*, 2020). Previous research has indicated that several clinical factors, including tumour size, Barcelona Clinic Liver Cancer (BCLC) stage, index normal ratio, total bilirubin, albumin, and treatment, may influence HCC prognosis (Wang P., *et al.*, 2022). In the study conducted by Le D.C. and Nguyen T.M., *et al.*, (2023), performance status, Child-Pugh score, and BCLC stage emerged as independent prognostic factors for HCC patient survival outcomes.

The main purpose of this study is to determine and compare the median survival times, assess the one-year survival rate and identify prognostic factors among patients with HCC in Hospital Pakar Universiti Sains Malaysia (HPUSM).The research finding may help in the management of HCC as well as to identify ways to improve the survival rate of this disease. Information on the survival rate is needed to measure whether we are in-line with other countries in HCC management.

## 1.2 Problem statement

Survival rate is crucial health indicators that helps evaluate diagnostic and therapeutic programs. To control the burden of cancer-related disease in any population, it is essential to understand its status, collect information about the incidence, survival, type and location of cancers, and record effective indicators on the process and survival of cancers in a monitoring area and patients' information. This

information is necessary to perform the correct and appropriate treatment and apply effective therapeutic methods and prevention strategies (Hassanipour *et al.*, 2020).

Despite advancements in preventative measures, screening techniques, and innovative technologies for diagnosis and treatment, the incidence and mortality rates of liver cancer persistently rise. There is still a significant knowledge gap regarding the survival rate and prognostic factors specific to the Kelantan population. Understanding the prognostic factors is essential for HCC control and prevention programs to improve the disease burden due to premature death (Azit *et al.*, 2022). This knowledge plays a vital role in clinical decision-making, patient counselling, resource allocation, and the patient management to improve the survival rates and overall well-being of HCC patients. These findings may also assist in identifying high-risk subgroups within the population affected by this cancer, serving as valuable references for future studies.

### 1.3 Significance of the study

This study was conducted at HPUSM in Kubang Kerian, Kelantan, to learn more about HCC patient survival in the local population. It's important to acknowledge that the study's findings may vary from those of similar studies in other countries due to differences in demographics, culture, beliefs, and lifestyle.

Conducting a research study focused on assessing the survival rate and median survival time can provide valuable insights into HCC. This investigation into prognostic factors related to survival aligns with both global Sustainable Development Goals (SDGs) and the 12th Malaysia Plan (RMK12), which aim to improve overall well-being, healthcare resource allocation, and healthcare research to enhance the survival prospects of HCC patients. It would be interesting to compare survival rates

across countries, especially in cases where the prognostic factors are similar to those found in Western nations and other Asian countries.

## 1.4 Research Question(s)

1. What is the median survival time of hepatocellular carcinoma (HCC) among patients in HPUSM?
2. What are the median survival times across group based on sociodemographic, clinical characteristics, laboratory findings and treatment modalities?
3. What are the prognostic factors associated with the survival rate among HCC patients in HPUSM?

## 1.5 Objectives

### 1.5.1 General objective

To determine the median survival time, compare the median survival times across group based on sociodemographic, clinical characteristics, laboratory findings and treatment modalities and the prognostic factors among HCC patients in Hospital Pakar USM.

### 1.5.2 Specific objectives

1. To estimate the median survival time of HCC among patients in HPUSM.
2. To compare median survival times across group based on sociodemographic, clinical characteristics, laboratory findings and treatment modalities.
3. To identify the prognostic factors that associated with the survival rate among HCC patients in HPUSM.

## 1.6 Hypothesis statement

The prognostics factors that associated with the survival among HCC patients in HPUSM are socio-demographic characteristics, clinical characteristics, laboratory finding and treatment modalities.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Literature search strategies

The literature search was conducted using search engines such as Google Scholar, ScienceDirect, and PubMed to identify articles related to the survival and prognostic factors among HCC patients. The search strategy included phrase searching, citation searching, and the use of Boolean operators. Phrases used in phrase searching were "survival of hepatocellular carcinoma" and "prognostic factors of hepatocellular carcinoma". Combinations of relevant keywords, including "HCC" AND "survival rates AND "Malaysia", "HCC" AND "prognostic factors" AND "Cox" and "HCC" AND "prognostic factors" AND "Cox". All identified articles were then imported into Mendeley Reference Manager for further review and citation management.

## 2.2 Liver cancer

The liver, one of the largest and most vital organs in the body, is located in the upper right side of the abdomen within the rib cage. It consists of two lobes and performs essential functions, including bile production for fat digestion, glycogen storage for energy, and detoxification of harmful substances from the blood, which are then eliminated through urine and stool (National Cancer Institute, 2022).

Liver cancer, a malignancy originating in liver cells, is a significant global health concern. It is categorized into primary and secondary liver cancer. Primary liver cancer develops within the liver tissue, while secondary (or metastatic) liver cancer occurs when cancer cells from other organs, such as the colon, breast, lung, or

pancreas, spread to the liver. Secondary liver cancer often indicates an advanced stage of primary cancer and is associated with poor prognosis (American Cancer Society, 2020).

Among primary liver cancers, HCC is the most prevalent, accounting for approximately 90% of cases (Bristol M.S., 2023). HCC is strongly associated with achronic liver diseases, particularly hepatitis B, hepatitis C, and cirrhosis. It is the seventh most frequently diagnosed cancer globally and the second leading cause of cancer-related mortality (Globocan, 2020). The highest incidence rates are reported in Asia and Africa, with Mongolia recording 93.7 new cases per 100,000 individuals annually. China has the largest number of HCC cases worldwide, primarily due to its high incidence rate of 18.3 cases per 100,000 individuals and its large population of 1.4 billion people (McGlynn, Petrick & El-Serag, 2021).

Aside from HCC, other types of primary liver cancer include intrahepatic cholangiocarcinoma, angiosarcoma, and hepatoblastoma, each with distinct characteristics. Intrahepatic cholangiocarcinoma (ICC), or bile duct cancer, arises from the bile ducts within the liver and accounts for 10 -15% of primary liver cancers. Due to its aggressive nature and lack of early symptoms, it is often diagnosed at an advanced stage. Angiosarcoma, a rare and highly aggressive cancer originating in the blood vessels of the liver, comprises less than 1% of liver cancers. It progresses rapidly, is often resistant to treatment, and has poor survival outcomes. Hepatoblastoma, an extremely rare liver cancer primarily affecting children under the age of three, accounts for about 1% of liver cancers (Rumgay H. *et al.*, 2021). Although these types of liver cancer are clinically significant, HCC remains the predominant form, making it the primary focus of research and clinical management (Llovet *et al.*, 2021).

In Malaysia, liver cancer is a major public health concern, particularly among males. According to the Malaysia National Cancer Registry Report 2012–2016, liver cancer ranked as the sixth most common cancer among Malaysian men, whereas its incidence among females was relatively low. A notable reduction in incidence rates was observed across all age groups compared to the 2007-2011 period (MOH, 2019). Despite this decline, liver cancer remains one of the leading causes of cancer-related deaths in Malaysia. Data from the World Health Organization (WHO) and Globocan (2022) indicate that liver cancer is among the top three causes of cancer mortality in the country.

## 2.3 Hepatocellular carcinoma: Risk factors and Clinical characteristics

HCC is recognized as the predominant primary liver malignancy and a major contributor to cancer-related fatalities worldwide, impacting individuals across different age groups. In the study by Ratana-Amornpin *et al.* (2021), it is highlighted that the Association of Southeast Asian Nations (ASEAN) region has the second highest incidence of HCC worldwide, following East Asia. They also noted that HCC incidence peaks around the age of 70 and is rare in individuals younger than 40. Its distribution varies geographically and is dependent on the etiology of underlying liver disease (Anugwom *et al.,* 2021).

Associated with underlying liver diseases, the development of nodules and tumours within the liver is linked to chronic inflammation and liver damage. Risk factors for HCC include heavy alcohol consumption, obesity, diabetes, and exposure to specific toxins. Typically arising in individuals with chronic liver conditions such as cirrhosis, hepatitis B (HBV) or C infections (HCV), excessive alcohol consumption and specific genetic conditions or other conditions causing prolonged liver damage,

HCC is associated with various factors contributing to liver cancer development (Asafo-Agyei KO and Samant H., 2023).

Cirrhosis, irrespective of its origin, is the most significant risk factor for HCC, with over 80% of HCC cases occurring in individuals with cirrhosis (Park S., *et al.*, 2024). The progression from cirrhosis to HCC is driven by chronic inflammation, repeated hepatocyte regeneration leading to DNA mutations, and hypoxia-induced angiogenesis (Reddy K. Rajender, *et al.*, 2023). Additionally, genetic alterations, such as mutations in tumor suppressor genes (e.g., TP53) and activation of oncogenic pathways, further promote carcinogenesis (Valiante, M. Grammatico P., *et al.*, 2023).

Currently, HBV and HCV are the primary global risk factors for HCC, although their significance is expected to decrease in the future. Asia bears the brunt of liver cancer cases, with 75% occurring in the region, primarily associated with HBV and HCV. HBV represents a major cause of liver disease-related mortality, especially in countries like China, India, and Nigeria (Devarbhavi *et al.*, 2023). Unfortunately, metabolic risk factors for HCC, including metabolic syndrome, obesity, type II diabetes, and non-alcoholic fatty liver disease (NAFLD), are increasing and may collectively become the primary cause of HCC worldwide. Persistent risk factors include excessive alcohol consumption and aflatoxin contamination in food crops in specific regions globally. NAFLD and alcohol-related liver disease are primary etiological factors in Western countries whereas HBV infection is the predominant culprit in Asia and Africa (Anugwom *et al.*, 2021).

The incidence and mortality rates of HCC are significantly influenced by ethnic and geographical differences, often resulting in a poor prognosis due to late diagnosis attributed to inadequate screening measures (Chavda *et al.*, 2023). The burden of HCC varies considerably among different ethnicities and regions, mirroring the

geographical distribution of HBV and HCV infections (Dasgupta *et al*., 2020). Notably, more than 80% of HCC cases occur in low-income countries, particularly in East Asia and sub-Saharan Africa, where high transmission rates of viral hepatitis prevail due to low socio-economic status (McGlynn, Petrick & El-Serag, 2021).

Several studies emphasize significant ethnic disparities in HCC incidence. Mahimpundu *et al.* reported a higher occurrence among African Americans than in Caucasian Americans (Chavda *et al.*, 2023). In the United States, there has been a noticeable increase in HCC incidence among Hispanic men, with a significant annual rise of 4.7% since 2000, surpassing rates observed in both non-Hispanic Caucasian and African-American populations (Ajayi *et al.*, 2020). Additionally, notable racial and ethnic disparities exist in HCC prognosis in the United States, with Black patients experiencing worse overall survival, while Hispanic and Asian patients have better overall survival compared to White patients (Rich *et al.*, 2022).

HCC is often diagnosed at an advanced stage for two primary reasons: early-stage patients may lack noticeable symptoms, and some clinicians may be hesitant to recommend surveillance for high-risk individuals (Jonathan M.S. and Robert L.C., 2023). In the initial phases, symptoms of liver cancer may not be apparent; however, as the disease progresses, individuals may experience manifestations such as unexplained weight loss, abdominal pain or swelling, jaundice, and fatigue. Most of the patients in Malaysia present late and were diagnosed at an intermediate and advanced stage (Raja M. and Yaacob Y., *et al*, 2021). Older age, advanced stage, severe liver disease and lower income was associated with a lower likelihood of receiving HCC treatment (Kim Y.A. *et al.*, 2021).

## 2.4 Median Survival Time of HCC patients

According to Le D.C and Nguyen T.M, *et al.* (2023), the median survival time reported in their studies was 10.0 months in Vietnam, aligning with similar studies in other countries, including Charonpongsuntorn's study in Thailand (OS was 8.9 months) and Wang and Li's study in China (9.0 months).

In contrast, Asian patients diagnosed with HCC demonstrated a notably superior median survival of 13 months, compared to 5 months for Non-Hispanic White patients (Wang Z. and Gu X., *et al.*, 2019). A similar trend was observed in Iran, where the overall median survival rate was reported to be 12.1 months (Sarveazad A., Agah S., *et. al.*, 2019). However, research by Hassanipour S. and Vali M., *et al.* in 2020 suggests that the liver cancer survival rate in Asian countries is comparatively lower than in Europe and North America, potentially due to differences in diagnostic facilities and a higher age at the recognition of the disease.

The median OS in Ethiopia was estimated to be 4.7 months. This finding aligns with the average survival time reported in sub-Saharan countries which is 4 months, as well as in China, where it is reported as 5 months. However, a study from Egypt in HCC patients showed an OS of 15 months (Abza G.B., Ahmed J.H., *et. al.*, 2023).

The variation in overall median survival across different regions underscores the influence of multiple prognostic factors on patient outcomes. Given this variability, it is essential to examine how specific sociodemographic, clinical, laboratory, and treatment-related variables contribute to survival differences in HCC patients. A comprehensive understanding of these factors is critical for optimizing patient management and improving outcomes.

Sociodemographic characteristics such as age, gender, and marital status have shown mixed associations with survival. Some studies suggest that younger patients

exhibit better survival due to more aggressive treatment approaches (Liu P.H., *et al.*, 2020), while others indicate that age alone is not a decisive prognostic factor (Kim Y., *et al.*, 2021). Gender disparities in survival have also been noted, with males typically experiencing worse outcomes, potentially due to higher exposure to risk factors such as HBV infection and alcohol consumption (Zhang X., *et al.*, 2023). Additionally, marital status has been linked to improved survival, likely due to increased social and financial support (Wu T., *et al.*, 2022); however, other studies suggest that broader social support networks may play a more significant role than marital status alone (Li J., *et al.*, 2021).

Among clinical characteristics, tumor size remains a major prognostic determinant, with smaller tumors (<5 cm) being associated with significantly longer survival (Li J., *et al.*, 2021). The impact of multifocal tumors on survival remains inconsistent, as some studies report poorer outcomes due to aggressive disease behavior, while others suggest that treatment strategies may mitigate this effect (Yang J.D., *et al.*, 2018). PVT is widely recognized as a marker of poor prognosis, often reducing median survival to less than six months due to its impact on treatment eligibility (Wu T., *et al.*, 2022). The presence of cirrhosis presents a complex prognostic factor, with some studies associating it with worsened survival due to compromised liver function, while others suggest that early diagnosis and close monitoring in cirrhotic patients may improve outcomes (Kim J.H., *et al.*, 2021).

Laboratory findings serve as crucial predictors of survival. Elevated AFP levels are consistently linked to reduced survival due to their association with aggressive tumor behavior (Liu J., *et al.*, 2020; Yang J.D., *et al.*, 2019). Similarly, increased AST and ALP levels are indicative of poorer prognosis, reflecting underlying liver damage and tumor burden (Fujiwara N., *et al.*, 2019; Kim, J.H., *et al.*, 2018). Elevated bilirubin

and INR further contribute to worse outcomes, as hyperbilirubinemia and coagulopathy indicate deteriorating hepatic function and higher mortality risk (Bruix J., *et al.*, 2019; Tandon P., *et al.*, 2020; Lee H.W., *et al.*, 2022). In contrast, ALT and APTT have not demonstrated consistent prognostic value, with studies indicating limited independent effects on survival outcomes (Wong G.L.H., *et al.*, 2021; Chen V.L., *et al.*, 2021).

Treatment modalities exert a profound influence on survival outcomes, with multimodal approaches yielding the most favorable results. Patients receiving a combination of locoregional and systemic therapies exhibit significantly longer median survival compared to those undergoing single-modality treatments or no treatment at all (Kudo M., *et al.*, 2023; Llovet J.M., *et al.*, 2022). Surgical resection combined with adjuvant therapies has been particularly effective in prolonging survival (Llovet J.M., *et al.*, 2022). Conversely, the absence of treatment is associated with a median survival of fewer than three months, highlighting the aggressive nature of HCC and the critical importance of timely therapeutic intervention (Marrero J.A., *et al.*, 2021).

Overall, these findings reinforce the necessity of an individualized, multidisciplinary approach to HCC management. Integrating sociodemographic, clinical, and biochemical prognostic factors into treatment decision-making can enhance survival prediction and guide evidence-based therapeutic strategies.

## 2.5 Survival Rate of HCC Patients

Survival rate refers to the proportion of individuals who remain alive at a specific time point after being diagnosed with or developing a particular disease or condition. It is typically expressed as a percentage over different time intervals, such

as one-year, five-year, or ten-year survival rates, providing insight into the expected survival duration for affected individuals (Rai S., Mishra P., and Ghoshal U.C., 2021).

This study primarily aims to evaluate the one-year overall survival rate among HCC patients. However, interpreting these findings requires comparison with previously reported survival rates across various timeframes. Survival rates for HCC vary widely across different regions, with substantial differences observed between Asian countries. A systematic review and meta-analysis by Hassanipour *et al.* (2020) found that the one-year, three-year, five-year, and ten-year survival rates for liver cancer in several Asian countries were 34.8%, 19%, 18.1%, and 4.1%, respectively**.** Japan reports the highest survival rates, while lower survival is observed in countries such as the Philippines, Thailand, India, and Singapore. Similarly, Villanueva (2019) noted that the five-year survival rate for HCC is approximately 18%, making it the second lowest among cancers, after pancreatic cancer.

Recent studies highlight regional variations in HCC survival rates. Wang C.Y. and Li S. (2019) reported survival rates in China of 49.3% at one year, 35.3% at two years, 26.6% at three years, and 19.5% at five years. In Vietnam, Le D.C., *et al.* (2023) found that survival at six months, one year, two years, and three years was 57.3%, 46.6%, 34.8%, and 29.7%, respectively. These findings indicate that HCC prognosis varies depending on healthcare access and treatment strategies in each country.

Outside of Asia, survival rates also differ. In Egypt, the one-year survival rate was 56%, while the three-year survival rate was 25%, with a significant proportion of cases diagnosed at an advanced stage (Abza G.B., Ahmed, J.H., *et al.* 2023). Meanwhile, in Ethiopia, HCC patients had one- and three-year survival probabilities of 26% and 8%, respectively. Although these findings provide a broader global

context, they underscore the importance of focusing on region-specific survival trends to improve patient outcomes. Table 2.1 presents a summary of overall survival rates.

**Table 2.1 Summary of studies reporting overall survival rates in HCC**

| Authors (Year) | Country | Study Design (n) | Survival rate (%) | | |
|---|---|---|---|---|---|
| | | | 1-yr | 3-yr | 5-yr |
| Le D.C., Nguyen T.M., *et. al.* (2023) | Vietnam | Retrospective Cohort Study (n=1,018) | 46.6 | 29.7 | - |
| Abza G.B., Ahmed J.H. (2023) | Egypt | Prospective Cohort Study (n=200) | 56.0 | 25.0 | - |
| Abza G.B., Ahmed J.H. (2023) | Ethiopia | Prospective Cohort Study (n=150) | 26.0 | 8.0 | - |
| Malaysia National Cancer Registry Report, 2017-2021 (2022) | Malaysia | Population-Based Cancer Registry | - | - | 12.8 |
| Kim Y.A., et. al. (2021) | South Korea | Retrospective Cohort Study (n=1,045) | 10.7 | - | - |
| Hassanipour S. and Vali M., et al. (2020) | Multiple Asian Countries | Systematic Review & Meta-Analysis (n=33,918) | 34.8 | 19.0 | 18.1 |
| Wang C.Y. and Li S. (2019) | China | Retrospective Cohort Study (n=2,887) | 49.3 | 26.6 | 19.5 |
| Azmawati M. N., & Krisnan R. (2012) | Malaysia | Retrospective Cohort Study (n=299) | 52.0 | 29.0 | 14.0 |

## 2.6 Prognostic Factors of HCC Patients

Prognostic factors in HCC are clinical, biological, and pathological variables that influence disease progression and patient survival. Identifying these factors is essential for predicting patient outcomes, guiding treatment strategies, and improving survival rates. HCC prognosis is influenced by multiple factors, including sociodemographic characteristics, clinical presentation, disease stage, laboratory

findings, and treatment modalities. Understanding these factors is crucial for predicting survival outcomes and optimizing patient management.

Sociodemographic factors, such as age and gender, can influence disease progression and treatment response. Clinical characteristics, including medical history, tumor stage, and comorbidities, play a critical role in determining survival. Laboratory markers, such as AFP and liver function tests, serve as important indicators of disease severity. Treatment modalities also significantly impact prognosis, with curative therapies offering better survival outcomes compared to palliative or no treatment. The Table 2.2 below summarizes key prognostic factors identified in various HCC studies and their impact on survival, as measured by hazard ratios.

**Table 2.2 Prognostic Factors and Their Impact on HCC Survival**

| Authors (Year) | Prognostic Factors | HR (95% CI) | p-value |
|---|---|---|---|
| Kim Y.A. *et al.* (2024) | Sex: Female | 0.94 (0.91 - 0.97) | - |
| | Comorbidities: Diabetes mellitus with complications | 0.92 (0.86 - 0.98) | - |
| Abza G.B. & Ahmed J.H. (2023) | Hepatitis B virus (HBV) treatment | 0.42 (0.22 - 0.79) | 0.007 |
| | Hepatitis C Virus (HCV) treatment | 0.67 (0.53 - 0.86) | 0.001 |
| Kwon M.J., *et. al.* (2023) | Serum AFP level ≥1,000 ng/mL | 1.53 (1.34 - 1.75) | < 0.001 |
| Ding J. *et. al.* (2021) | Age: 65 – 74 years | 1.27 (1.17 - 1.37) | <0.001 |
| | Sex: Male | 0.94 (0.91 - 0.97) | <0.001 |
| | Marital status: Married vs not married | 0.88 (0.86 - 0.91) | <0.001 |
| | Tumour size > 5cm | 2.51 (2.39 - 2.64) | <0.001 |
| | Multiple lesions without vascular invasion | 1.36 (1.31-1.42) | <0.001 |

Table 2.2 continued

| Authors (Year) | Prognostic Factors | HR (95% CI) | p-value |
|---|---|---|---|
| Sarveazad A., *et. al.* (2019) | Coinfection with HBV and HCV | 2.11 (1.81 - 4.6) | 0.036 |
| | Tumor size >3 cm | 3.06 (1.68 - 4.97) | 0.027 |
| | Involved lymph nodes >2 | 4.12 (2.66 - 6.38) | 0.001 |
| | Combination therapy with surgery and chemotherapy | 0.40 (0.15 - 0.79 | 0.023 |

### 2.6.1 Clinical Characteristics

The prognosis of HCC is influenced by various clinical characteristics, including patient history, underlying liver conditions, disease presentation, and tumor progression. Understanding these characteristics is essential for predicting disease progression, guiding treatment decisions, and improving survival outcomes.

A family history of liver cancer is a well-established risk factor for HCC. Individuals with an affected first-degree relative have a higher risk of developing the disease and often experience worse survival outcomes (An *et al.*, 2019). In addition to genetic predisposition, smoking has been strongly associated with an increased incidence of HCC and higher mortality rates, especially among individuals with underlying liver disease or chronic viral hepatitis (Luo *et al.*, 2021).

Comorbidities such as diabetes mellitus, hypertension, and dyslipidemia significantly impact HCC progression and survival. Diabetes mellitus has been recognized as both a risk factor for HCC development and an indicator of poor prognosis, although studies suggest that metformin use may reduce this risk (Campbell C., Wang T., *et al.*, 2021). Similarly, metabolic disorders, including obesity, hypertension, and dyslipidemia, contribute to the progression of HCC and have been linked to poorer overall survival (Simon T.G., King L.Y., *et al.*, 2018).

Beyond metabolic conditions, viral infections remain the most significant risk factor for HCC. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV)

infections contribute to liver inflammation and fibrosis, leading to an increased likelihood of developing HCC (Datfar *et al.*, 2021). Among HBV-related HCC patients, the presence of hepatitis B e antigen (HBeAg) and elevated HBV DNA levels has been associated with an increased risk of tumor recurrence and poorer survival outcomes (Asafo-Agyei & Samant, 2023). Furthermore, untreated HBV infection has been linked to a 3.5-fold higher mortality risk compared to patients receiving antiviral therapy, emphasizing the importance of HBV management in reducing HCC-related mortality (Abza, G.B & Ahmed, J.H., *et al*., 2023).

Patients with chronic liver disease, including cirrhosis and a history of liver abscess**,** face additional challenges in disease progression and treatment response. Cirrhosis, regardless of its underlying cause, worsens liver function and limits treatment options, leading to lower survival rates (Wang Z. and Gu X., *et al.*, 2019). Additionally, a history of liver abscesses has been associated with a higher risk of liver malignancies, further complicating prognosis and long-term survival outcomes (Liang By, Xiong M., *et al.*, 2021).

The clinical presentation of HCC varies among patients but is often indicative of disease severity. Symptoms such as abdominal pain, abdominal mass, distension, and discomfort are frequently observed in patients with advanced-stage HCC, suggesting tumor progression, vascular invasion, or hepatic decompensation (Zhang Y.F., Shi M., *et al.*, 2021). Furthermore, systemic symptoms, including loss of appetite, unintentional weight loss, and jaundice**,** indicate worsening disease and are associated with poorer overall survival (Wang F., Gao S., *et al.*, 2023). Additionally, hepatomegaly and splenomegaly are commonly observed in advanced disease stages, reflecting extensive liver involvement and portal hypertension, which further

contribute to disease progression and mortality risk (Singal A.G., Parikh N.D., *et al.*, 2019).

To accurately assess prognosis and guide treatment, staging systems such as the Child-Pugh classification and the Barcelona Clinic Liver Cancer (BCLC) system are indispensable. The Child-Pugh classification is widely used to assess hepatic function, categorizing patients into Class A (well-compensated), Class B (moderate impairment), and Class C (severe dysfunction) (Zhang Y.F., Shi M., *et al.*, 2021). Patients in Child-Pugh class B or C exhibiting significantly worse survival outcomes than those in class A due to increased hepatic decompensation and limited treatment options (Zhang Y.F., Shi M., *et al.*, 2021). Alongside Child-Pugh, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely adopted clinical classification system, categorizing HCC into five stages (0, A, B, C, D), each with distinct survival expectations and treatment recommendations (Llovet J.M., Bru C, *et al.*, 1999). Other staging systems, such as the Model for End-Stage Liver Disease (MELD), tumor–node–metastasis (TNM), and Okuda staging systems**,** are also utilized to stratify patients based on prognosis and assist in treatment planning (Singal A.G., Parikh N.D., *et al.*, 2019).

In addition to disease staging, tumor characteristics such as size, number of nodules, and the presence of portal vein tumor thrombosis (PVTT) significantly affect survival outcomes. Tumor characteristics further determine disease progression and survival in HCC patients. Larger tumors (>5 cm) and the presence of multiple tumor nodules have been linked to significantly lower survival rates (Wang Z. & Gu X., *et al.*, 2019). Additionally, PVTT is one of the most aggressive features of HCC, often leading to high recurrence rates and poor survival outcomes (Sarveazad A., Agah S.,

*et al*., 2019). PVTT obstructs liver blood flow and complicates treatment options, significantly worsening patient prognosis (Ferrante N.D., Pillai A., 2020).

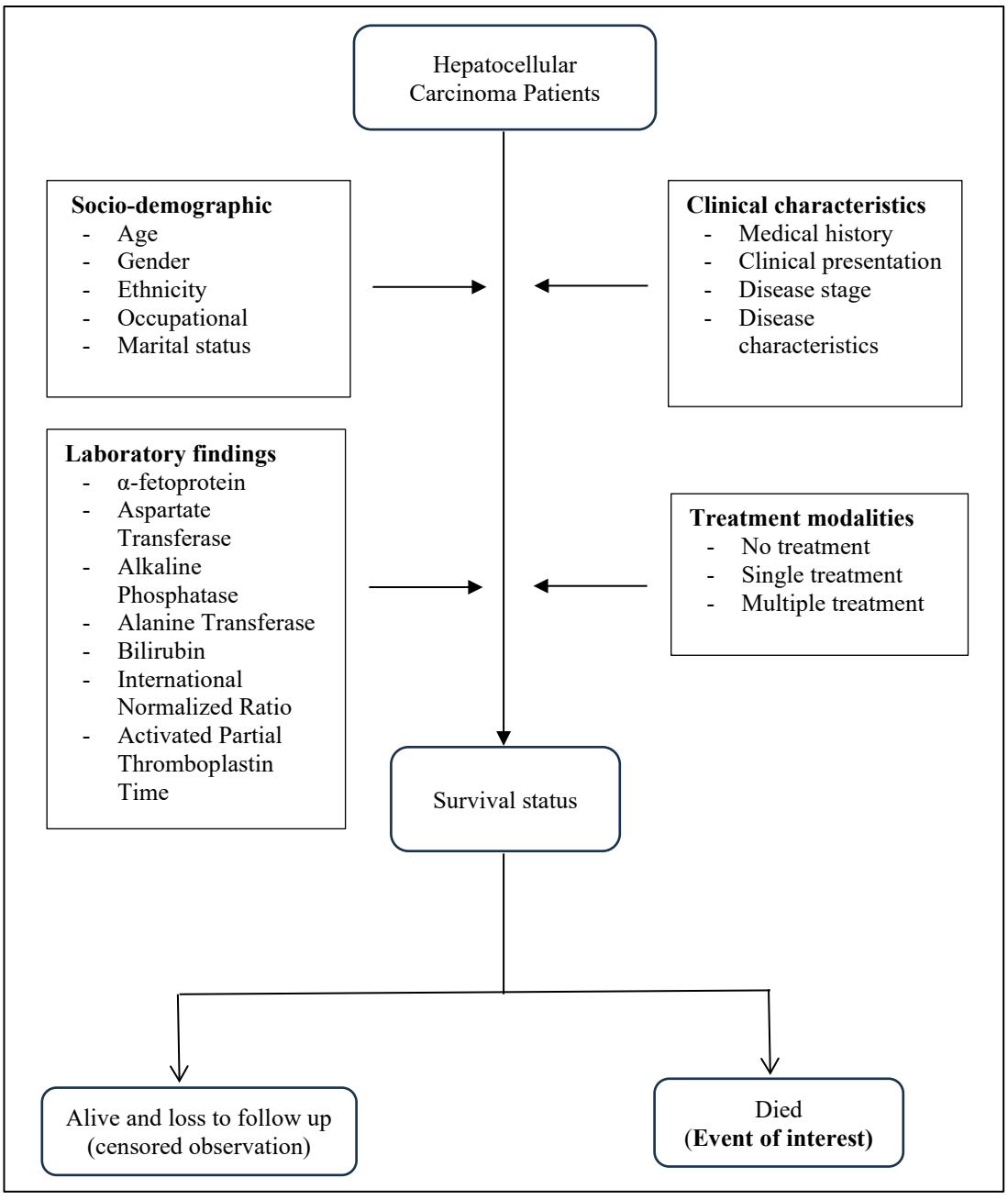


Figure 2.1 Conceptual framework of the study

### 2.6.2 Laboratory Findings

Laboratory biomarkers play a crucial role in assessing disease severity, treatment response, and survival outcomes in HCC patients. Among them, AFP has been widely used as a tumor biomarker, though it is elevated in only about two-thirds of HCC cases. Beyond its role in diagnosis, elevated AFP levels are associated with poorly differentiated tumors and an increased risk of recurrence following liver resection and transplantation, making it a significant prognostic factor (Lee W.C., 2019). A recent study identified high levels of AFP, total bilirubin, and fibrinogen as independent risk factors for poor survival in HCC patients, reinforcing their prognostic value (Xu L., *et al.*, 2023).

Liver function tests, including AST and ALT, are widely used to assess liver health. A higher AST/ALT ratio has been correlated with poorer overall survival, making it an independent predictor of disease progression (Fu J., Jiang J., *et al.*, 2023). Similarly, elevated levels of ALP have been associated with advanced HCC and poorer prognosis, likely due to their role in indicating tumor invasion and liver dysfunction.

In addition, total bilirubin is a key marker of liver function impairment, with higher bilirubin levels being linked to lower survival rates in HCC patients (Xu J., *et al.*, 2023). Coagulation parameters such as the INR and APTT are also crucial indicators of liver dysfunction. Abnormalities in these values suggest progressive liver disease and are correlated with worse survival outcomes. Taken together, these laboratory findings serve as essential prognostic indicators for predicting patient outcomes, guiding treatment strategies, and optimizing clinical management in HCC.

### 2.6.3 Treatment Modalities

Over the past two decades, the treatment landscape for HCC has evolved significantly, introducing a range of therapeutic options to improve survival outcomes.

Curative treatments such as surgery and liver transplantation remain the cornerstone for early-stage HCC. At the same time, locoregional therapies like TACE continue to play a key role in managing intermediate-stage disease (Jafri W. and Kamran M., 2019). For patients with portal vein tumor thrombus, effective and safe treatment options include surgery, TACE, radiotherapy, and combination therapies, all of which have demonstrated success in prolonging survival and enhancing the quality of life (Luo F., Li M., Ding J., *et al.*, 2021). Although TACE is a noncurative option, it has been shown to elicit objective responses in 16% to 70% of patients, with a median survival of approximately 26 months (Ferrante N.D., Pillai A., 2020). Advancements in the management of advanced HCC have introduced multiple systemic therapies, offering sequential treatment strategies that can extend survival by up to two years. Additionally, recent data suggest that a broader patient population may benefit from surgical interventions beyond early-stage disease, particularly with the refinement of treatment selection criteria (Jafri W. and Kamran M., 2019).

A study by Wang Z. and Gu X., *et al.* (2019) highlighted significant differences in treatment patterns and survival outcomes among Asian HCC patients. Their analysis of 1,284 patients revealed that Asians were more likely to undergo chemotherapy and surgery (tumor destruction or resection) than unmatched non-Hispanic White patients but had lower rates of radiation therapy. The study also found that radiation reduced mortality risk by 29%, chemotherapy by 37%, and surgery—particularly liver transplantation—by up to 85%. Similarly, research by Abza G. B., Ahmed J. H., *et al.* (2023) emphasized that HCC survival outcomes depend heavily on treatment choice, highlighting the need for patient-specific therapeutic strategies to optimize survival and quality of life.

# CHAPTER 3

# METHODOLOGY

## 3.1 Research Design

The retrospective cohort was applied in which patients' medical records was reviewed and important information on variables of interest and patients' survival status were collected and recorded.

## 3.2 Study Duration

This study was conducted from 25th February 2024 until 21st July 2024.

## 3.3 Study Area

This study was conducted at Hospital Pakar Universiti Sains Malaysia (HPUSM) located in Kelantan.

## 3.4 Study Population

### 3.4.1 Reference population

The reference population was all Hepatocellular Carcinoma patients in Kelantan.

### 3.4.2 Source population

The source population was all patients diagnosed with HCC at HPUSM located in Kelantan from 1st January 2012 to 31st December 2021.

### 3.4.3 Sampling frame

The sampling frame was all the patients diagnosed with HCC in HPUSM from 1st January 2012 to 31st December 2021 (recruitment phase of the patients) which is 120 months based on inclusion and exclusion criteria as listed below. An additional follow up period was from 1st January 2022 until 31st December 2023 (24 months).

#### 3.4.1(a) Inclusion criteria

- Patients diagnosed with HCC (ICD 10 code: C22) from 2012 to 2021.
- Aged 18 years or older.
- HCC was diagnosed by typical radiologic characteristic findings of multiphasic computed tomography (CT) scan, or dynamic contrast-enhanced magnetic resonance imaging (MRI), or confirmed by pathology.

#### 3.4.1(b) Exclusion criteria

- Non – Malaysian citizen.
- Diagnosis with malignancies other than HCC

## 3.5 Sample size estimation

Sample size for this study was calculated based on objective of the study.

### 3.5.1 Sample size estimation for Objectives 3

The sample size for this study was determined using survival analysis (hazard ratio) and analysed with the log-rank test using Power and Sample Size Calculation (PS) software (Dupont & Plummer, 1997). The key parameters for sample size calculation are provided in Table 3.1.